Remarks

Claims 1-16 are pending in the subject application. By this Amendment, Applicant has amended claims 1, 9, and 15. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-16 are currently before the Examiner and favorable consideration of the pending claims is respectfully requested.

The disclosure in the specification has been objected to in view of typographical errors and on the grounds that the title is not descriptive. Applicant gratefully acknowledges the Examiner's careful review of the subject specification. Applicant notes that the specification has now been amended at page 10, line 1, to correct the typographical error. In addition, Applicant has amended the title of the subject specification in accordance with the Examiner's suggestion. Entry of the amendments and withdrawal of the objection is respectfully requested.

Claim 15 is rejected under 35 USC §112, second paragraph, as indefinite. Applicant has amended claim 15 to recite "said chimeric monoclonal antibody." Basis for this language can be found in claim 9, from which claim 15 depends. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 1-8 are rejected under 35 USC §112, first paragraph, as nonenabled by the subject specification. The Examiner asserts that the subject specification, while being enabled for a humanized monoclonal antibody or antigen-binding fragments retaining the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody, is not enabled for a humanized monoclonal antibody that does not contain all six CDRs and does not retain the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody. By this Amendment, Applicant has amended claim 1 to refer to "the hypervariable regions." Thus, Applicant respectfully submits that the humanized antibody of claim 1 as amended comprises all six hypervariable regions (CDRs) derived from the high affinity non-rodent, non-human monoclonal antibody. Applicant respectfully submits that the humanized antibody would retain the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody and, therefore, claims 1-8 of the subject invention are enabled. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

Claims 1, 2, and 4-7 are rejected under 35 USC §102(e) as anticipated by Queen *et al.* (U.S. Patent No. 5,530,101) on the grounds that the Queen *et al.* patent teaches humanized monoclonal antibodies comprising CDRs from a rabbit monoclonal antibody, and human framework and constant regions wherein the humanized monoclonal antibodies have antigen binding affinities stronger than 10^{10}1/mol. The Examiner directs the applicant to column 10, lines 55-65, which states "...have binding affinities of at least about 10^8 l/mol, preferably 10^9 l/mol to 10^{10} l/mol or stronger". Applicant respectfully traverses this ground of rejection.

Applicant respectfully asserts that the Queen *et al.* patent does not teach or suggest Applicant's claimed invention. As the Examiner is aware, in order to anticipate, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). Applicant respectfully asserts that an antibody having a binding affinity of "10^{10} 1/mol, or stronger" does not meet the limitation of the antibody of claim 1 having "an antigen binding affinity of at least about 10^{11} 1/mol, . . ." (emphasis added). That the Queen *et al.* patent states in its general disclosure that an antibody has a binding affinity of "10^{10} 1/mol, or stronger" does not establish that the reference teaches an antibody having at least 10^{11} 1/mol binding affinity. There is no evidence in the Queen *et al.* patent of an antibody having an antigen binding affinity of at least about 10^{11} 1/mol. Accordingly, Applicant respectfully asserts that the Queen *et al.* patent does not teach each and every element of Applicant's claimed invention and, therefore, does not anticipate the rejected claims. Reconsideration and withdrawal of the rejection under 35 USC §102(e) is respectfully requested.

Claims 1-8 are rejected under 35 USC §103(a) as obvious over Groves *et al.* (1989) in view of Ehrlich *et al.* (1983) and Queen *et al.* (U.S. Patent No. 5,530,101) and Steward *et al.* (1983). In addition, claims 9-16 are rejected under 35 USC §103(a) as obvious over Groves *et al.* (1989) in view of Ehrlich *et al.* (1983) and Morrison (1985) and Steward *et al.* (1983). The Examiner asserts that the Groves *et al.* reference teaches high affinity ovine monoclonal antibodies (produced from mouse x sheep heterohybridomas) for therapeutic use and the high affinities of ovine monoclonal antibodies is one advantage of non-rodent over rodent antibodies. The Examiner also asserts that the Groves *et al.* reference teaches heterohybridomas as a starting point for the production of engineered

antibodies to improve effector functions including antibodies that combine components from two or more species. The Examiner asserts that the Ehrlich *et al.* reference teaches that the use of a sheep anti-digoxin Fab fragment is limited to life-threatening situations due to its immunogenicity in humans. The Queen *et al.* patent is cited for teaching humanized monoclonal antibodies comprising CDRs from a non-rodent, non-human monoclonal antibody (*i.e.*, rabbit monoclonal antibody) and human framework and constant regions wherein the humanized monoclonal antibodies have antigen-binding affinities stronger than 10^{10} M^{-1} (l/mol), are less immunogenic in human patients and that because the effector portion is human, humanized antibodies interact better with the human immune system. The Steward *et al.* reference is cited as teaching that the art recognized that high antibody affinity is superior to lower antibody affinity in terms of mediating a number of biological functions, such as neutralization of toxins, virus neutralization, protection against bacterial infections, complement fixation *(i.e.*, effector function), *etc.*, which are clearly mechanisms that are exploited in passive immunotherapy. The Morrison reference is cited as teaching chimeric antibodies comprising non-human variable regions and human constant regions and that chimeric antibodies should exhibit the effector function associated with the human constant regions and should be less antigenic in humans than are totally non-human antibodies. Applicant respectfully traverses these grounds of rejection.

Applicants will address both §103 rejections together since both share reliance on the Groves *et al.* (1989), Ehrlich *et al.* (1983), and Steward *et al.* (1983) references. It is well established in patent law that the Patent Office bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. This burden can be satisfied only by showing some objective teaching in the prior art or that knowledge generally available to a person of ordinary skill in the art would lead that artisan to combine the relevant teachings of the references. Applicant notes that the title of the Groves *et al.* reference is "The Production and Application of a Non-Rodent Monoclonal Antibodies in Veterinary Science" (emphasis added). The Groves *et al.* reference discloses only the use of the monoclonal antibodies for use in the veterinary field and no humanized or chimeric antibodies containing human regions are taught or suggested therein. Reference to the use of non-rodent antibodies (such as sheep or cow) in the Groves *et al.* publication are solely in relation to their use in veterinary medicine and, therefore, the Groves *et al.* reference provides no motivation to one skilled

in the art to employ any humanization technique (the purpose being to make the antibodies more compatible for human, not veterinary, use) to make the non-rodent/human chimeric antibodies of the present invention. In addition, Applicant notes that the Groves *et al.* reference is published in the journal *Veterinary Immunology and Immunopathology*; thus, an ordinarily skilled artisan is even less likely to combine the teaching of this article with other references to arrive at the humanized antibodies of the present invention.

An obviousness analysis requires that the prior art both suggest the claimed subject matter and provide a reasonable expectation of success to an ordinarily skilled artisan in arriving at an applicant's claimed invention. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicant indicated in regard to the rejection under 35 USC §102(e) that the Queen *et al.* patent differs from the present invention in that it does not specifically teach humanized or chimeric antibodies having non-rodent variable regions with binding affinities of at least 10^{11} l/mol. The Stewart *et al.* reference is relied on by the Examiner to teach that the art recognized that higher antibody affinity is superior to lower antibody affinity in terms of mediating a number of biological reactions. The Ehrlich *et al.* reference teaches that the use of sheep anti-digoxin Fab is limited to life threatening situations due to the adverse immunological reactions associated with their administration.

Applicant respectfully asserts that the Examiner has failed to provide sufficient evidence to support a *prima facie* case of obviousness. Even assuming, *arguendo*, that a person of ordinary skill in the art recognized that high antibody affinity is desirable, and that non-human antibodies can elicit undesirable immunological reactions, and that the skilled artisan may have considered trying to reduce the immunogenicity of the ovine monoclonal antibodies of the Groves *et al.* reference by using the humanization techniques from the Queen *et al.* patent, Applicant respectfully asserts that an ordinarily skilled artisan would not have had the required reasonable expectation of success at the time of the present invention to obtain a humanized monoclonal antibody having a non-rodent portion and an antibody binding affinity of at least 10^{11} l/mol. Non-rodent antibody binding affinity is dependent upon various factors, such as the nature of the antigen to which the antibody is raised, and the structure of the variable region of the antibody. See, for example, the enclosed Queen *et al.* (1989) reference, in particular, at page 10033, column 1, therein. As demonstrated by the Queen *et*

al. (1989) reference, there is unpredictability in the art that has particular bearing on the "reasonable expectation of success" of obtaining a non-rodent antibody and antigen binding affinity of at least 10^{11} l/mol.

In regard to the rejection of claims 9-16 under 35 USC §103(a) as obvious over Groves *et al.* (1989) in view of Ehrlich *et al.* (1983) and Morrison (1985) and Steward *et al.* (1983), the Examiner asserts that the Morrison reference teaches chimeric antibodies comprising non-human variable regions and human constant regions, and that chimeric antibodies should exhibit the effector function associated with the human constant regions and should be less antigenic in humans than are totally non-human antibodies. Applicant respectfully asserts that the Morrison reference differs from the present invention in that it does not specifically teach or suggest humanized or chimeric antibodies having non-rodent variable regions with binding affinities of at least 10^{11} l/mol. As stated previously herein, the Queen *et al.* patent demonstrates that antigen binding affinity associated with non-rodent antibodies is unpredictable as it is dependent upon various factors, such as the nature of the antigen to which the antibody is raised and the structure of this variable region of the antibody. Thus, a person of ordinary skill in the art would not have had the required reasonable expectation of success in producing chimeric antibodies with binding affinities of at least 10^{11} l/mol. As such, Applicant respectfully asserts that the claimed invention is not obvious over the cited references.

Applicant respectfully notes that claims in parent application Serial No. 08/425,682, which are identical to the claims in the subject application, were held by the Board of Patent Appeals and Interferences to be nonobvious over references by Queen *et al.*, Groves *et al.*, Ehrlich *et al.*, Steward *et al.*, and Morrison. The Ehrlich *et al.*, Steward *et al.*, and Morrison references cited in the instant Office Action are the same references cited in the §103 rejections appealed in the parent application. The Groves *et al.* reference and the Queen *et al.* patent cited in the instant Office Action, while not identical to the Groves *et al.* and Queen *et al.* references cited in the parent application, pertain to and disclose subject matter very similar to the references cited in the rejections in the parent application. For example, the Groves *et al.* references cited in the instant Office Action and in the parent application both concern high affinity ovine monoclonal antibodies (heterohybridomas). Similarly, the Queen *et al.* references cited in the instant Office Action and in the parent application

both pertain to humanized monoclonal antibodies that bind to a human interleukin 2 receptor (see the claims of the Queen *et al.* patent and see the title of the Queen *et al.* reference). A copy of the Board's decision on appeal is enclosed with this Amendment. In their decision, the Board stated that the Patent Office had not established a *prima facie* case of obviousness on the grounds that the cited references did not provide the required reasonable expectations of success in arriving at Applicant's claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachment: copy of Queen *et al.* (1989) reference
Petition and Fee for Extension of Time Under 37 CFR §1.136(a)
Information Disclosure Statement Under 37 CFR §§1.97 and 1.98
Form PTO/SB/08(1 page)
Copies of references cited therein (8 references)
Copy of the Board's decision on appeal for application Serial No. 08/425,682